Remarks

Claims 37-50 and 60-63 have been canceled without prejudice. Claims 22, 33 and 35 have been amended to correct typographical errors noted by the Examiner. No new matter has been added.

The Examiner indicated that a reference listed on a Form PTO-1449 filed by Applicant was not considered (and was crossed out) because the publication date was not provided. The Examiner also indicated that the reference (Nuttall et al.) would be considered if Applicant provided the publication date. It is not clear if Applicant needs to submit a new PTO-1449 form for this reference. If so, Applicant respectfully requests that the Examiner advise of same. However, if not, then Applicant provides the full reference citation including the publication date herewith: Nuttall et al., FEBS Lett. 2002 Apr 10;516(1-3):80-86.

Objections to the Disclosure and Substitute Specification

The Examiner identified a number of defects in the specification and made certain objections thereto.

Applicant encloses a substitute specification. Added text is indicated by double underlining to distinguish it from single underlined text already in the application. Deleted text is indicated by strikethrough or double bracketing.

Applicant has amended the specification to correct typographical errors and to include changes made in prior related applications of which this application claims the benefit.

A marked-up copy of the specification and claims are also enclosed with a statement under 37 CFR 1.125(b) verifying that no new matter has been added.

Applicant respectfully requests withdrawal of the objections to the specification.

Drawings

Applicant submits herewith a corrected Fig. 7A.

Rejections Under 35 U.S.C. §112

The Examiner rejected claims 18-22, 25-27, 31-33, 35 and 51-54 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement, indicating that the rejection is a new matter rejection.

The Examiner indicated that the originally filed specification discloses immunoglobulins comprising two heavy chains sufficient for the formation of an antigen binding site.

Applicant respectfully traverses the rejection for the reason that the claims do not contain new matter. Applicant provides herewith support for the claims as presented. The locations of the support (page and line numbers) are provided using the clean version of the replacement specification filed herewith.

For example, on page 11, line 27 to page 12, line 8, Applicant stated:

The invention further relates to a fragment of an immunoglobulin which has been described hereabove and especially to a fragment selected from the following group:

a fragment corresponding to one heavy polypeptide chain of an immunoglobulin devoid of light chains, ...

a fragment of at least 10 preferably 20 amino acids of the variable region of the immunoglobulin, or the complete variable region, especially a fragment corresponding to the isolated V_{HH} domains or to the V_{HH} dimers linked to the hinge disulphide,

On page 18, lines 8-9, Applicant describe the production of variable region (V_{HH}) an expression system.

Under laboratory conditions, V_{HH} regions are produced in the Immuno PBS vector in mg amounts per liter.

On page 20, lines 21-22, Applicant described that the disclosed fragments (e.g., V_{HH}) can be used to prepare immunoglobulins or derivatives of immunoglobulins.

Furthermore, starting from the immunoglobulins of the invention, or from fragments thereof, new immunoglobulins or derivatives can be prepared.

On page 21, lines 3-5, Applicant described combination molecules that can be prepared using the fragments of immunoglobulins:

The immunoglobulins of the invention allow further the preparation of combined products such as the combination of the heavy-chain immunoglobulin or a fragment thereof with a toxin, an enzyme, a drug, a hormone.

On page 21, line 15 to page 22, line 18, Applicant described the production of hetero-antibodies such as multifunctional, e.g. bifunctional, antibodies. In particular, the paragraph spanning pages 21-22 and the first full paragraph of page 22 describes the serial cloning of two V_{HH} genes in an expression vector for production of a hetero-specific polypeptide.

The latter half of page 22 describes labeling of the polypeptides of the invention, including fragments of the antibodies. In particular, the last paragraph on page 22 describes one of the advantages of using V_{HH} fragments in this way:

In these applications the small size of the V_{HH} fragment is a definitive advantage for penetration into tissue.

On page 23, lines 14-16, Applicant described modified four-chain immunoglobulin molecules in which V_H regions are partially replaced by V_{HH} sequences:

The invention also relates to a modified 4-chain immunoglobulin or fragments thereof, the V_H regions of which has been partialy replaced by specific sequences or amino acids of heavy chain immunoglobulins, especially by sequences of the V_{HH} domain.

The first half of page 24 describes the cloning and expression by viral vectors of one or two V_{HH} genes.

The working example beginning on page 36 describes the cloning, expression and purification of a V_{HH}. The results of the expression and purification are shown in Fig. 8.

Therefore, contrary to the Examiner's assertion that the specification does not support the claims, resulting in the claims containing new matter, the specification in fact provides ample description of the claimed subject matter.

Accordingly, withdrawal of the rejection of claim(s) 18-22, 25-27, 31-33, 35 and 51-54 under 35 U.S.C. §112 is respectfully requested.

Rejections Under 35 U.S.C. § 102

1. The Examiner rejected claims 18-22, 25-27, 31-33, 35 and 51-53 under 35 U.S.C. § 102(b) as being anticipated by the Ungar-Waron et al. reference, as evidenced by Hamers-Casterman et al., and as evidenced by EP 0 739 981 A1 and Roux et al. Applicant respectfully traverses the rejection.

Contrary to the Examiner's assertion that Ungar-Waron teaches a "40 Kd IgG", the Ungar-Waron reference merely teaches a 40 kDa band; it does not teach that the 100 kDa or 40 kDa bands are immunoglobulin molecules. Rather, Ungar-Waron refers to the 40 kDa band as "an additional protein band" (see p. 200), not an immunoglobulin. On page 202 of the Ungar-Waron reference, the authors refer again to the fact that camel serum contains "*a complex IgG-like protein associated with an additional molecule of approximately 100,000 daltons AMW.*"

(emphasis added). The complex is said to dissociate into three proteins bands, corresponding to "γ- *and L-like chains and a protein band of about 40,000 AMW*" (emphasis added). Applicant notes that from the comments contained in the publication that neither the protein band of about 100 kDa nor the protein band of about 40 kDa are suggested to belong to an immunoglobulin species, contrary to the others in the complex, which are identified as an "IgG-like" protein.

In addition to not teaching the identity of the 100 kDa and 40 kDa bands, the Ungar-Waron reference does not enable the skilled person to identify the proteins. The methods used for protein isolation are not specific for IgG. Other proteins are also isolated when using the described methods. A later publication (Azwai et al. J Comp Pathol. 109(2):187-95, 1993, of record) could not achieve identification of this band.

The conditions used by Ungar-Waron include precipitation with 50% ammonium sulfate followed by separation of the constituents of the serum. Precipitation with ammonium sulfate is not specific for immunoglobulins. It is, rather, a precipitation agent for proteins in general, used to concentrate proteins, not to purify them. In Ungar-Waron, this precipitation is followed by ion exchange chromatography (DEAE chromatography). This method allowed proteins other than Igs to be present in the fractions eluted from the DEAE Sephacel column.

This means that the skilled person, trying to reproduce the teaching of Ungar-Waron, could not know the nature of the product that was sought and therefore would have had to try an unknown number and types of protocols in order to achieve the separation of a band of 40 kD, and even then would not be certain that the correct protein had been obtained. Ungar-Waron does not provide a disclosure that enables the skilled person to inevitably reach the same result.

In view of the clear deficiencies of the teachings of Ungar-Waron, any conclusion that the protein bands produced by Ungar-Waron were heavy chain immunoglobulins is not only the result of an ex post facto analysis, but moreover is plainly incorrect.

The other references cited, none of which are prior art against the instant application, do not serve as evidence of the identity of the protein bands of Ungar-Waron. There is no way to

know if the 100 kDa and 40 kDa bands of Ungar-Waron are the same as the 100 kDa and 46/43 kDa bands of Hamers-Casterman.

Accordingly, withdrawal of this rejection is respectfully requested.

2. The Examiner rejected claims 18-22, 25-27, 31-33, 35 and 51-53 under 35 U.S.C. § 102(b) as being anticipated by the Prelli and Frangione reference as evidenced by Hamers-Casterman et al.

The Examiner states that the Prelli and Frangione reference describes an IgH that has a "normal V region amino terminal sequence followed by an internal deletion of the remaining V and the entire CH1 domains..."

That is incorrect – the reference does not state that the V region is "normal". The Prelli and Frangione reference describes a particular heavy chain disease protein called BUR. The BUR protein is stated to have a "complete V region, hinge, CH_2 and CH_3 domains" (see Abstract and third paragraph of Discussion section). No mention of the "normality" of the V region was made.

Importantly, the Prelli and Frangione reference makes no mention of the ability of the BUR protein to bind an antigen of interest. There is no evidence whatsoever, in the reference itself or in the Hamers-Casterman et al reference, that heavy chain disease proteins bind antigen. Applicant notes that binding an antigen of interest is an essential feature of the claimed invention.

Therefore, the Prelli and Frangione reference does not disclose an invention as claimed. Accordingly, withdrawal of this rejection is respectfully requested.

3. The Examiner rejected claims 18-22, 25-27, 31-33, 35 and 51-53 under 35 U.S.C. § 102(b) as being anticipated by the Hamers-Casterman et al. reference as evidenced by EP 0 739 981 A1.

Applicant has indicated above, in response to the rejection made under 35 U.S.C. § 112, where the specification provides support for the claimed invention, such that there is not new matter in the claims. Accordingly, Applicant is entitled to the priority date of the application, which removes the Hamers-Casterman et al. reference as prior art effective against the claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 18-22, 25-27, 31-33, 35 and 51-54 under 35 U.S.C. § 103(a) as being unpatentable over the Hamers-Casterman et al. reference in view of the Schlom reference.

Applicant has indicated above, in response to the rejection made under 35 U.S.C. § 112, where the specification provides support for the claimed invention, such that there is not new matter in the claims. Accordingly, Applicant is entitled to the priority date of the application, which removes the Hamers-Casterman et al. reference as prior art effective against the claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Claim Objections

The Examiner objected to claims 22, 33 and 35, for typographical errors in the claims. Applicant has amended the claims to correct these errors. With respect to the objection to claim 22, Applicant notes that there is no antecedent basis for "CH1 domain" in claim 19, and therefore

adding the word "the" to claim 22 is improper. Instead, Applicant has amended claim 22 to refer to "a CH1 domain".

Accordingly, withdrawal of the objections is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
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